International Journal of Surgery 12 (2014) 329–333

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original research

Efficacy of combination of 0.2% GTN and lignocaine ointments in wound healing and pain relief after Milligan Morgan hemorrhoidectomy – A comparison with lignocaine and 0.2% GTN ointments separately

Khizar Ishtiaque Khan [a,*], Ahmed Waqas [b], Muhammad Akmal [c], Shahid Mahmood [d], Afaq Iqbal [e]

[a] Buraidah Central Hospital, Buraidah, Saudi Arabia
[b] HIT Hospital, Taxilla, Pakistan
[c] CMH, Lahore, Pakistan
[d] CMH, Malir, Pakistan
[e] CMH, Bannu, Pakistan

ARTICLE INFO

Article history:
Received 8 June 2013
Received in revised form
25 October 2013
Accepted 17 January 2014
Available online 29 January 2014

Keywords:
Milligan Morgan hemorrhoidectomy
GTN
Lignocaine

ABSTRACT

Objective: To compare the analgesic efficacy and rate of wound healing of combination of 0.2% Glyceryl Trinitrate and 2% lignocaine ointments with 0.2% Glyceryl Trinitrate and 2% lignocaine ointment separately after Milligan Morgan hemorrhoidectomy.
Design: Randomized control trial.
Place and duration of study: Combined Military Hospital, Kharian, Malir and Bannu. November 2007 to August 2011.
Patients and methods: Patients undergoing Milligan Morgan hemorrhoidectomy were randomized into 3 groups by using computer generated table. Group A received combination of 0.2% Glyceryl Trinitrate and 2% lignocaine ointment, Group B 2% lignocaine and Group C received 0.2% Glyceryl Trinitrate ointment. These ointments were given on twice daily basis. Pain scores were measured on a 100 mm Visual Analog Scale. Pain scores and quantity of oral analgesics used were compared daily until the 7th post-operative day. The time required for complete healing (in weeks) was also compared.
Results: Out of 210 patients, 192 (67 Group A, 64 Group B and 61 Group C) completed the study. Demographic data were comparable in all three groups. There were statistically significant reductions in pain scores and quantity of analgesics used from the first to the fourth post-operative days in Group A. The time required for complete healing was also significantly reduced in the combination group. There were no significant side effects in any group.
Conclusion: The combination of 0.2% GTN and 2% lignocaine showed better pain relief resulting in less use of oral analgesics and faster healing of the wound after Milligan Morgan hemorrhoidectomy.

1. Introduction

Hemorrhoidectomy had become a gold standard procedure for 3rd and 4th degree hemorrhoids [1]. Post-hemorrhoidectomy pain remains a major concern to patients as well as to the surgeons. Many patients prefer to live with the symptoms of hemorrhoids rather than undergo surgery, mainly because of post-hemorrhoidectomy pain [2]. Different treatment modalities to minimize post-hemorrhoidectomy pain have been evaluated. Anal dilatation [3] and internal sphincterotomy [4,5] had shown some promising results but are invasive procedures which may cause flatus incontinence due to irreversible sphincter damage. Narcotics and non-steroidal anti-inflammatory drugs (NSAIDs) may be quite beneficial but they usually require a high dosage, resulting in more known gastrointestinal side effects [6]. Many topical preparations have also been used quite successfully, namely nifedipine [7], botulinum toxin [8,9], metronidazole [2,10,11], sucralfate [3,12] and lignocaine [13]. Local infiltration of lignocaine [14] and flavonoids

* Corresponding author.
E-mail address: khizarikhan@yahoo.com (K.I. Khan).

1743-9191/$ – see front matter
http://dx.doi.org/10.1016/j.ijsu.2014.01.013

[15] has been. Many studies have evaluated the analgesic efficacy of 0.2% GTN ointment on post-hemorrhoidectomy pain. As yet, there is no consensus due to headaches and conflicting results. To date, no study has compared 0.2% GTN, 2% lignocaine and the combination of both for post-hemorrhoidectomy pain. We compared the efficacy of combination of 0.2% Glyceryl Trinitrate (GTN) and 2% lignocaine ointments with both the constituents (0.2% GTN and 2% lignocaine ointment) separately to evaluate their effects on post-procedure pain and healing time [4,16,17].

2. Methodology

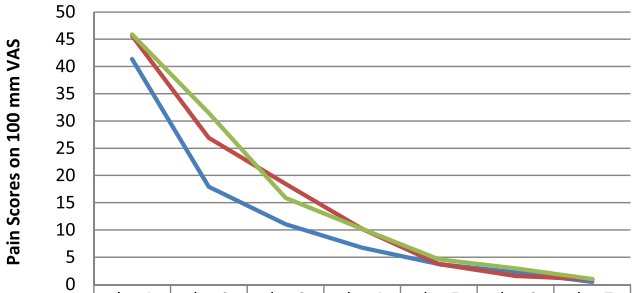
This was a multicenter double blind, prospective, randomized control trial conducted at Combined Military Hospital, Kharian, Malir and Bannu, Pakistan from November 2007 to August 2011. Inclusion criteria were: patients above 18 years of age of both genders and undergoing surgery for 3rd or 4th degree hemorrhoids (according to the American Society of Colon and Rectum Surgery Classification [18]). Exclusion criteria were: pregnancy or lactation, any other concomitant perianal pathology warranting surgery, patients with cardiovascular pathology, patients taking nitrates or calcium channel blockers, patients allergic to GTN, lignocaine or any of their components and poor general condition (ASA IV or V). All the patients undergoing study were informed about the aims and protocol of the study and written consent was obtained. The ethical committees of all the three hospitals approved the study protocol. Eligible patients were randomly assigned to one of the three treatment groups according to a computer generated list using random allocation software. A minimum of 210 patients (70 in each group) were required (calculated by computer generated software/calculator by feeding the required fields) to detect an α significance level of 0.05 with 80% power. Group A received a combination of 0.2% GTN and 2% lignocaine ointment; in Group B the patients were given 2% lignocaine ointment and in Group C 0.2% GTN ointment was given to the patients. The combination of 0.2% GTN and 2% lignocaine as well as 0.2% GTN ointment was prepared in white soft paraffin by the hospital dispenser and placed in the similar containers. All the patients underwent standard Milligan Morgan hemorrhoidectomy by a consultant surgeon at each center either under regional (spinal) or general anesthesia as per choice of the anesthetist. All the patients had standardized post-operative care. They were advised to take sitz baths in lukewarm water for at least 10 min twice daily (from 1st post-operative day and onwards), once in the morning preferably after passing stools and again before going to bed. They were also advised to apply the prescribed ointment with the fingertip circumferentially 1 cm inside the anal canal, each time after taking the sitz bath. Stool softeners were also advised to be taken (lactulose 30 ml twice daily) from the 1st post-operative day until complete wound healing. All the patients were given 75 mg intramuscular diclofenac sodium 12 hourly on operation day and were advised to take oral codeine phosphate and paracetamol (Tablet Codogesic, Wilson's Pharmaceutical company, Pakistan) when required. Patients were discharged after 24 h as per protocol, on individual basis. Patients were given a follow up proforma and were instructed to chart pain scores on a 00 mm (no pain) to 100 mm (worst pain ever) visual analog scale (VAS) and asked to note down the total number of analgesics taken on daily basis. Pain scores were taken daily, preferably after defecation. Any complication occurring especially headache, fever and/or excessive purulent discharge from the wound were recorded and reported immediately to the responsible surgeon. Headache was noted on 100 mm VAS on daily basis (00–30 Mild; 30–50 Moderate; >50 mm Severe). Patients were followed up on weekly basis from the 3rd to 6th week post-operatively. Their pain scores as well as the total number of analgesics taken were noted. The double blinding was ensured by not disclosing the treatment group to the patient and to the surgeon who examined the patients on each visit and recorded the data. All the patients were examined for complete wound healing and or any other complication on each visit and their proforma was checked for any error and advised accordingly. Complete wound healing was defined as complete epithelialisation of the wound. Data were analyzed on SPSS 16 and one way ANOVA was applied for pain scores, total analgesics used and rate of complete healing. *P* value of ≤ 0.05 with a confidence interval of 95% was considered as significant.

3. Results

A total of 210 patients were enrolled in the study (70 in each group), out of which 192 patients completed the study. The demographic data and grades of hemorrhoids were comparable within the groups (Table 1). All the patients were initially available for the baseline evaluation. At the end of 6 weeks, 67 patients from the combination group (A), 64 from the lignocaine group (B) and 61 from the GTN group (C) were available for the final assessment. The main reason for loss to follow-up was moving to other cities. A total number of 9 (4.68%) patients fell into this category (5 from combination group and 4 from GTN group). There were 5 patients who suffered from severe headache (3 in combination group and 2 in GTN group) and dropped out. The remaining 4 (2.08%) patients became unwilling during the course of follow up, due to personal reasons (1 from lignocaine group and 3 from GTN group). The difference in the pain scores was significant between the combination group and the two other groups from 1st to 4th post-operative days ($p < 0.05$). The mean pain scores on VAS in combination group were 41.34, 17.91, 11.04 and 6.72 on day 1,2,3 and day 4 respectively. The pain scores in lignocaine group were 45.62, 26.88, 18.44 and 10.16 and in GTN group 45.9, 31.48, 15.9 and 10.16 on days 1, 2, 3 and 4 respectively. Whereas there was only significant difference between the lignocaine and the GTN groups on 2nd post op day ($p = 0.016$), mean pain score on VAS was 26.88 and 31.48, respectively. The effect of treatment on pain scores is shown in Fig. 1. The number of oral analgesics used on daily basis in each group was given in Table 2. There was a significant difference in the use of analgesics between combination group and the lignocaine and GTN groups on 1st, 2nd and 3rd post op days only ($p < 0.05$). There was no significant difference in the use of analgesics between lignocaine and GTN groups ($p > 0.05$). Patients in the combination group had a mean healing time of 4.45 weeks as compared to 4.48 weeks for 0.2% GTN group and 5.07 weeks for 2% lignocaine group. The difference was highly significant between the combination group and the lignocaine group ($p < 0.001$) as well as between GTN and lignocaine groups ($p < 0.001$). There was no significant difference between combination and GTN groups ($p = 0.892$). These data suggest that GTN was the main differentiating factor amongst all the three groups as far as healing time was concerned. The healing

Table 1
Demographic and clinical characteristics of patients.

Group	Age in years	Male	Female	Degree of hemorrhoids	
				3rd	4th
A (Combination)	41.16 ± 10.072	30 (44.77%)	37 (55.27%)	46 (68.7%)	21 (31.3%)
B (2% Lignocaine)	43.36 ± 8.543	34 (53.1%)	30 (46.9%)	49 (76.6%)	15 (23.4%)
C (0.2% GTN)	41.72 ± 9.306	30 (49.2%)	31 (50.8%)	43 (70.5%)	18 (29.5%)



	day 1	day 2	day 3	day 4	day 5	day 6	day 7
Group A	41.34	17.91	11.04	6.72	3.73	2.24	0.45
Group B	45.62	26.88	18.44	10.16	3.75	1.56	0.94
Group C	45.9	31.48	15.9	10.16	4.59	2.95	0.98

Fig. 1. Effect of treatment on pain scores.

rates are given in Table 2. 13 patients (6 from combination group and 7 from GTN group) reported to have headache, out of which 5 patients had to be dropped from the study due to the severe headache, 3 (4.48%) from combination group and 2 (3.27%) from GTN group.

4. Discussion

Pain after hemorrhoidectomy remained a concern to both the patient and the operating surgeon. Achieving better pain control usually demands parenteral analgesia which did not permit it to be carried out as a day case procedure and as a result increasing the overall cost of treatment [19]. Anal manometry had shown hypertonia in patients with hemorrhoids and the surgical insult caused a further increase in the spasm [20]. This spasm or increase in the resting anal pressure of internal anal sphincter (IAS) may be a major causative factor in post hemorrhoidectomy pain.

Apart from traditional analgesics, many novel treatments had been tried with their own merits and demerits. Topical lignocaine ointment had shown slightly better pain relief but did not decrease the use of analgesics and there was also no improvement in the healing rates [20]. GTN being a donor of Nitrous Oxide (NO) – a smooth muscle relaxant, has been successfully used in treatment of chronic anal fissure and had also shown promising results in faster healing of post hemorrhoidectomy wound [21–23]. GTN was found to relieve post hemorrhoidectomy pain significantly due to relaxation of the IAS. This decrease in the spasm also resulted in better blood supply and decrease in the ischemia of the perianal region thus improving healing [5,24]. Despite the use of 0.2% GTN in post hemorrhoidectomy patients, pain was not significantly reduced [6,25] so the need for oral analgesics in the form of either NSAIDs or narcotic analgesics remained substantial [5]. In order to minimize the use of oral analgesics we studied the analgesic efficacy of the combination of 2% lignocaine and 0.2% GTN ointment. The secondary objective was to evaluate the effect of this combination on the healing rates.

In our study the gender distribution as well as the mean age was comparable to other studies [26,27] as well as within the groups. The grades of hemorrhoids were also comparable within the groups as well as with other studies [2]. After a careful search no authenticated data was found in which combination of 0.2% GTN with 2% lignocaine ointment was compared either with placebo or any other treatment modality.

One of the objectives of our study was to compare the analgesic efficacy of all the three groups. The difference in the pain scores was statistically significant between the combination group and the lignocaine group from 1st to 4th post-operative days. This difference decreased to minimum and became statistically insignificant from the 5th post op day onwards. When the results between the combination group and the 0.2% GTN group were compared the difference in the pain scores was statistically significant from the 1st to 3rd post-operative day but this difference was less pronounced as compared to the difference between the combination group and the lignocaine group. Lastly when the pain scores between the lignocaine group and the GTN group were compared the difference was statistically significant from 1st to 3rd post-operative days only. This overall result could be explained on the basis of the pathophysiology of post-hemorrhoidectomy wounds. The surgical insult was known to be the main causative factor in increasing the IAS thus increasing the pain in the initial post-operative period. GTN being a NO donor decreased this spasm and a better pain relief was achieved which was augmented by the addition of topical lignocaine ointment. As the healing started this spasm tends to decrease so the additional effect of GTN was minimized and the difference in pain scores between the groups became insignificant. So by combining the topical anesthetic with a NO donor/IAS relaxant the pain scores were reduced in the initial post-operative period. This initial post-operative pain remained to be the most troublesome feature of hemorrhoidectomy for both the patient and the treating surgeon [19]. Most of the surgeons opted for parenteral analgesics during this time period which not only abolished the chances of performing hemorrhoidectomy as a day case procedure but had also resulted in over treatment of pain by prescribing parenteral analgesics. This combination being a topical application minimized the demand of parenteral analgesia and thus can be helpful for advocating hemorrhoidectomy as a day care procedure.

Silverman et al. compared topical diltiazem with placebo in a randomized controlled trial instead of GTN as IAS relaxant and showed better pain relief after hemorrhoidectomy in the early post op period [27]. Another study by Patti and colleagues supported the findings of Silverman by performing anal manometry in patients suffering from hemorrhoids and found to have increase in resting IAS tone, this resting tone of IAS remained elevated even after hemorrhoidectomy in the initial post-operative period [19]. We did not perform anal manometry and our results were based on subjective findings only. Anal manometry is suggested in future studies to confirm the effects of the combination of GTN and lignocaine in post hemorrhoidectomy patients. In another study the combination of topical nifedipine (calcium channel blocker) and lignocaine had been compared with topical lignocaine alone but it showed no significant difference in the time of rescue analgesia and use of oral analgesics [2]. The only difference found to be significant was in the perception of pain at 6 h and on the 7th post-operative day, which was better in the treatment group. In another randomized trial, the difference in pain scores as well as rescue analgesia were not significant between GTN and placebo but the sample size was small and a larger sample size and meta-analysis would be required to confirm the findings [28]. Tan and colleagues also showed no significant difference in pain scores and use of analgesics between GTN and the placebo [29]. These findings were in contrast to our study and further studies are required to compare the results.

The other objective of the study was to evaluate the difference of use of oral analgesics in the three treatment groups. We advised all the patients to take oral paracetamol and codeine phosphate (Codogesic) in case of pain from the 1st post-operative day onwards and to record the number of tablets used daily in the 1st post-operative week. The total number of analgesics being used in all the three groups was given in Table 2. We did not compare the results on the operation day because we gave intramuscular diclofenac sodium 12 hourly to all the patients. So the difference in pain scores as well as the use of analgesics on operation day could not be compared with other studies. The difference in the use of

Table 2
Time taken for complete healing and oral analgesics used.

Group	Complete healing mean ±SD	Oral analgesics used (frequency)						
		1st POD	2nd POD	3rd POD	4th POD	5th POD	6th POD	7th POD
A (Combination)	4.45 ± 0.744	81	59	29	11	4	2	1
B (2% Lignocaine)	5.08 ± 0.762	110	80	47	18	9	4	4
C (0.2% GTN)	4.51 ± 0.744	95	71	43	20	11	2	1

*POD=Post-Operative Day.

Table 3
Comparison of groups for complete healing and pain scores.

Groups compared	Complete healing[a] (*p* value)	Post OP daily pain scores[b] (*p* value)						
		1st POD	2nd POD	3rd POD	4th POD	5th POD	6th POD	7th POD
Combination & GTN	0.892	0.034	0.000	0.008	0.037	0.766	0.744	0.617
Combination & lignocaine	0.000	0.046	0.000	0.000	0.035	1.0	0.760	0.661
GTN & lignocaine	0.000	0.988	0.016	0.269	1.0	0.779	0.335	0.996

[a] Complete healing in Weeks.
[b] *p* value by comparing pain scores TAKEN on 100 mm VAS.

total number of analgesics was statistically significant on the 2nd and 3rd post-operative days only between the combination group and the lignocaine group. The difference in the use of analgesics was only significant on 2nd post-operative day between the combination group and the GTN group as well as between lignocaine group and the GTN group. There was no difference between the three groups in the use of oral analgesics on the 1st post-operative day. It was presumed and was later confirmed by a detailed interview/discussion with the concerned patients that most of the patients were quite apprehensive about post-operative pain, especially on the 1st post-operative day and their threshold to take analgesics was very low and some of them even took the analgesics preemptively. This drawback of the study could be overcome either by conducting the study as an inpatient for the first post-operative week or to strictly instruct the patients not to take any analgesic until a specified pain severity had been reached. Only a few studies had shown the same results when topical GTN had been used [30]. Whereas in other randomized controlled trials there was no difference in the use of oral analgesics between topical GTN group and the placebo group [27,28,30]. All these studies had either compared topical GTN or topical nifedipine instead of comparing the combination of GTN and lignocaine with either placebo or any other topical application so a true comparison could not be done.

The secondary objective of the study was to evaluate the added advantage of GTN in form of faster healing rates. GTN had shown better healing rates in treatment of Chronic Anal Fissure (CAF) [31,32] and a number of studies had also shown its beneficial effects on wound healing after Milligan Morgan hemorrhoidectomy [27,33]. The wound healing was found to be rapid in patients using GTN in a study conducted by Karanlik et al., in which the rate of complete healing at the end of 3rd week was 76.7% in the Nitroglycerine Group as compared to 46.7% in the placebo group [30]. In our study, complete healing was defined as complete epithelialization of the wound. The ointments containing GTN showed faster healing than the lignocaine group as the difference in healing rates was statistically significant between the combination group and the lignocaine group and also between the GTN group and the lignocaine group (Table 3). There was no difference in the healing rates between the combination group and the GTN group. So the presence of NO donor in the form of GTN resulted in better healing rates. It was also observed that better analgesia and faster healing also resulted in early return to work and normal activity thus indirectly being beneficial in terms of financial burden to the community and the state. These observations can be confirmed by conducting another study (see Table 4).

Headache remained the major limiting factor in the use of topical GTN in CAF or post hemorrhoidectomy patients [7,34]. In our study fewer patients experienced headache but the severity was also mild to moderate. Mild headache was experienced by 5 patients whereas 3 patients had moderate headache. Only 5 patients were dropped from the study due to severe headache (3 from the combination group and 2 from the GTN group). A larger number of patients experiencing relatively severe headache in other studies was most probably due to the use of GTN in higher concentrations (0.4%) or when the patients were advised to use it on thrice daily basis [35,36]. In most studies in which 0.2% GTN was prescribed on twice daily basis patients had less headache and minimal dropouts. We advised our patients to use 0.2% GTN twice daily, once in the morning preferably after defecation and the second dose just before going to bed. The timing of this application especially just before going to bed might also have resulted in lesser frequency and severity of headache.

In a few studies the topical treatment was started immediately after surgery which resulted in better pain relief in the first 24 h post-operatively as less parenteral analgesia was administered [8,37]. In our study we prescribed intramuscular diclofenac sodium 75 mg 12 hourly to all the patients and the topical treatment was started from the 1st post-operative day onwards. This was because a few patients undergoing surgery under general anesthesia were not able to apply the ointment on the operative day and failed to follow the required protocol due to obvious reasons so this benefit

Table 4
Comparison of groups for Use of analgesics.

Groups compared	Analgesics used (*P* value)						
	1st POD	2nd POD	3rd POD	4th POD	5th POD	6th POD	7th POD
Combination & GTN	0.010	0.032	0.014	0.086	0.099	0.996	0.998
Combination & lignocaine	0.000	0.003	0.005	0.273	0.340	0.622	0.275
GTN & lignocaine	0.373	0.727	0.951	0.820	0.779	0.687	0.323

of the treatment group could not be compared with other studies and another study may be conducted to evaluate its analgesic efficacy in the initial 24 h post-operatively.

5. Conclusion

It is safely concluded that the combination of topical lignocaine and 0.2% GTN had better analgesic efficacy from 1st post op day to 4th post op day.

It can also safely be concluded that the combination of GTN and lignocaine and GTN ointment alone had faster healing rates as compared to lignocaine ointment alone in cases of Milligan Morgan hemorrhoidectomy. The side effects were also not the limiting factor when the dosage and its timing were adjusted on twice daily basis.

Ethical approval

The ethical approval was given by the ethical committees of all the respective hospitals.

Funding

There are no source of funding for this research.

Author contribution

1. Dr Khizar Ishtiaque Khan – Principal Author and investigator at CMH Bannu and CMH Malir.
2. Dr Ahmed Waqas – Study Design, Pilot project and Data analysis.
3. Dr Muhammad Akmal – Investigator at CMH Kharian.
4. Dr Shahid Mahmood – Investigator at CMH Malir.
5. Dr Afaq Iqbal – Investigator at CMH Bannu.

Conflicts of interest

There are no conflict of interests.

References

[1] P.J. Nisar, J.H. Scholefield, Managing haemorrhoids, BMJ 327 (2003) 847–851.
[2] P. Perrotti, P. Dominici, E. Grossi, R. Cerutti, C. Antropoli, Topical nifedipine with lidocaine ointment versus active control for pain after hemorrhoidectomy: results of a multicentre, prospective, randomized, double-blind study, Can. J. Surg. 53 (1) (2010 Feb) 17–24.
[3] J.C. Goligher, N.G. Graham, F.T. De Dombal, G.R. Giles, S.G. Clark, The value of stretching of anal sphincters in the relief of pain after haemorrhoidectomy, Br. J. Surg. 56 (1969) 390.
[4] I. Kanellos, E. Zacharakis, E. Christoforidis, S. Angelopoulos, D. Kanellos, M.G. Pramateftakis, et al., Usefulness of lateral internal sphincterotomy in reducing postoperative pain after open hemorrhoidectomy, World J. Surg. 29 (4) (2005 April) 464–468.
[5] S.K. Asfar, T.H. Juma, T. Ala-Edeen, Hemorrhoidectomy and sphincterotomy. A prospective study comparing the effectiveness of anal stretch and sphincterotomy in reducing pain after hemorrhoidectomy, Dis. Colon Rectum 31 (3) (1988 Mar) 181–185.
[6] E.T. Goldstein, P.R. Williamson, S.W. Larach, Subcutaneous morphine pump for postoperative hemorrhoidectomy pain management, Dis. Colon Rectum 36 (5) (1993 May) 439–446.
[7] M.R. Siddiqui, C. Abraham-Igwe, A. Shangumanandan, V. Grassi, I. Swift, A.M. Abulafi, A literature review on the role of chemical sphincterotomy after Milligan-Morgan hemorrhoidectomy, Int. J. Colorectal Dis. 26 (6) (2011 Jun) 685–692.
[8] J. Davies, D. Duffy, N. Boyt, A. Aghahoseini, D. Alexander, S. Leveson, Botulinum toxin (botox) reduces pain after hemorrhoidectomy: results of a double-blind, randomized study, Dis. Colon Rectum 46 (8) (2003 Aug) 1097–1102.
[9] R. Patti, P.L. Almasio, M. Arcara, S. Sammartano, P. Romano, C. Fede, et al., Botulinum toxin vs. topical glyceryl trinitrate ointment for pain control in patients undergoing hemorrhoidectomy: a randomized trial, Dis. Colon Rectum 49 (11) (2006 Nov) 1741–1748.
[10] P. Tranqui, D.C. Trottier, C. Victor, J.B. Freeman, Nonsurgical treatment of chronic anal fissure: nitroglycerin and dilatation versus nifedipine and botulinum toxin, Can. J. Surg. 49 (1) (2006 Feb) 41–45.
[11] T.J. Nicholson, D. Armstrong, Topical metronidazole (10 percent) decreases posthemorrhoidectomy pain and improves healing, Dis. Colon Rectum 47 (5) (2004 May) 711–716.
[12] J.J. Puche, M.J. García-Coret, F.L. Villalba, I. Ali-Mahmoud, J.V. Roig, Local treatment of a chronic anal fissure with diltiazem vs. nitroglycerin. A comparative study, Cir. Esp. 87 (4) (2010 Apr) 224–230.
[13] J.M. Shiau, H.P. Su, H.S. Chen, K.C. Hung, S.E. Lin, C.C. Tseng, Use of a topical anesthetic cream (EMLA) to reduce pain after hemorrhoidectomy, Reg. Anesth. Pain Med. 33 (1) (2008 Jan) 30–35.
[14] J.M. Shiau, K.C. Hung, H.H. Chen, W.H. Chen, Y.H. Wu, C.C. Tseng, Combination of topical EMLA with local injection of lidocaine: superior pain relief after Ferguson hemorrhoidectomy, Clin. J. Pain 23 (7) (2007 Sep) 586–590.
[15] T. Colak, T. Akca, M. Dirlik, A. Kanik, A. Dag, S. Aydin, Micronized flavonoids in pain control after hemorrhoidectomy: a prospective randomized controlled study, Surg. Today 33 (11) (2003) 828–832.
[16] E.T.C. Milligan, C.N. Morgan, L.E. Jones, R. Officer, Surgical anatomy of the anal canal and operative treatment of hemorrhoids, Lancet 2 (1937) 1119–1124.
[17] S. Dhawan, S. Chopra, Nonsurgical approaches for the treatment of anal fissures, Am. J. Gastroenterol. 102 (6) (2007 Jun) 1312–1321.
[18] Page 635, module 15.5, disorders of anal canal Robert J.C. Steele, Kenneth Cambell, in: Alfred Cuschieri, Robert J.C. Steele, Abdool Rahim Moossa (Eds.), Essential of Surgical Practice (Higher Surgical Training in General Surgery), fourth ed., 2002.
[19] H.J. Wasvary, J. Hain, M. Mosed-Vogel, P. Bendick, D.C. Barkel, S.N. Klein, Randomized, prospective, double-blind, placebo-controlled trial of effect of nitroglycerin ointment on pain after hemorrhoidectomy, Dis. Colon Rectum 44 (8) (2001 Aug) 1069–1073.
[20] R. Patti, P.L. Almasio, V.M. Muggeo, S. Buscemi, M. Arcara, S. Matranga, et al., Improvement of wound healing after hemorrhoidectomy: a double-blind, randomized study of botulinum toxin injection, Dis. Colon Rectum 48 (12) (2005 Dec) 2173–2179.
[21] S. Frank, H. Kämpfer, C. Wetzler, J. Pfeilschifter, Nitric oxide drives skin repair: novel functions of an established mediator, Kidney Int. 61 (3) (2002 Mar) 882–888.
[22] M.B. Witte, A. Barbul, Role of nitric oxide in wound repair, Am. J. Surg. 183 (4) (2002 Apr) 406–412.
[23] K. Ratnasingham, M. Uzzaman, S.M. Andreani, D. Light, B. Patel, Meta-analysis of the use of glyceryl trinitrate ointment after haemorrhoidectomy as an analgesic and in promoting wound healing, Int. J. Surg. 8 (8) (2010) 606–611.
[24] R. Bhardwaj, M.C. Parker, Modern perspectives in the treatment of chronic anal fissures, Ann. R. Coll. Surg. Engl. 89 (5) (2007 Jul) 472–478.
[25] R. Shalaby, A. Desoky, Randomized clinical trial of stapled versus Milligan–Morgan haemorrhoidectomy, Br. J. Surg. 88 (8) (2001 Aug) 1049–1053.
[26] H. Ortiz, J. Marzo, P. Armendáriz, M. De Miguel, Stapled hemorrhoidopexy vs. diathermy excision for fourth-degree hemorrhoids: a randomized, clinical trial and review of the literature, Dis. Colon Rectum 48 (4) (2005 Apr) 809–815.
[27] R. Silverman, P.J. Bendick, H.J. Wasvary, A randomized, prospective, double-blind, placebo-controlled trial of the effect of a calcium channel blocker ointment on pain after hemorrhoidectomy, Dis. Colon Rectum 48 (10) (2005 Oct) 1913–1916.
[28] C. Elton, P. Sen, A.C. Montgomery, Initial study to assess the effects of topical glyceryl trinitrate for pain after haemorrhoidectomy, Int. J. Surg. Investig. 2 (5) (2001) 353–357.
[29] K.Y. Tan, K.K. Sng, K.H. Tay, J.H. Lai, K.W. Eu, Randomized clinical trial of 0.2 per cent glyceryl trinitrate ointment for wound healing and pain reduction after open diathermy haemorrhoidectomy, Br. J. Surg. 93 (12) (2006 Dec) 1464–1468.
[30] H. Karanlik, R. Akturk, H. Camlica, O. Asoglu, The effect of glyceryl trinitrate ointment on posthemorrhoidectomy pain and wound healing: results of a randomized, double-blind, placebo-controlled study, Dis. Colon Rectum 52 (2) (2009 Feb) 280–285.
[31] R. Nelson, Nonsurgical therapy for anal fissure, Cochrane Database Syst. Rev. 4 (2006 Oct 18) CD003431.
[32] O.M. Jones, Towards safer treatments for benign anorectal disease: the pharmacological manipulation of the internal anal sphincter, Ann. R. Coll. Surg. Engl. 89 (6) (2007 Sep) 574–579.
[33] D.Y. Hwang, S.G. Yoon, H.S. Kim, J.K. Lee, K.Y. Kim, Effect of 0.2 percent glyceryl trinitrate ointment on wound healing after a hemorrhoidectomy: results of a randomized, prospective, double-blind, placebo-controlled trial, Dis. Colon Rectum 46 (7) (2003 Jul) 950–954.
[34] E. Karamanlis, A. Michalopoulos, V. Papadopoulos, A. Mekras, D. Panagiotou, A. Ioannidis, et al., Prospective clinical trial comparing sphincterotomy, nitroglycerin ointment and xylocaine/lactulose combination for the treatment of anal fissure, Tech. Coloproctol. 14 (Suppl. 1) (2010 Nov) S21–S23.
[35] E.A. Carapeti, M.A. Kamm, P.J. McDonald, S.J. Chadwick, D. Melville, R.K. Phillips, Randomised controlled trial shows that glyceryl trinitrate heals anal fissures, higher doses are not more effective, and there is a high recurrence rate, Gut 44 (5) (1999 May) 727–730.
[36] C.S. Richard, R. Gregoire, E.A. Plewes, R. Silverman, C. Burul, D. Buie, et al., Internal sphincterotomy is superior to topical nitroglycerin in the treatment of chronic anal fissure: results of a randomized, controlled trial by the Canadian Colorectal Surgical Trials Group, Dis. Colon Rectum 43 (8) (2000 Aug) 1048–1057.
[37] F. El Tinay Oel, S.Y. Guraya, The use of 0.2% glyceryl trinirate oinment for anal fissures, Saudi J. Gastroenterol. 11 (1) (2005 Jan) 40–44.